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(54) Title: ADVANCED QUINOLINONE BASED PROTEIN KINASE INHIBITORS

(57) Abstract: Hydroxy carboxy quinolinone based derivatives have enhanced and unexpected drug properties as inhibitors of protein kinases and are useful in treating disorders related to abnormal protein kinase activities such as cancer.

ADVANCED QUINOLINONE BASED PROTEIN KINASE INHIBITORS

Description

Field of Invention:

The invention relates to protein kinase inhibitors and to their use in treating disorders related to abnormal protein kinase activities such as cancer and inflammation. More particularly, the invention relates to hydroxyl carboxy quinolinone based derivatives and their pharmaceutically acceptable salts employable as protein kinase inhibitors.

Background:

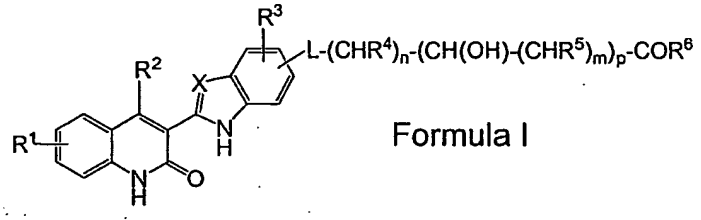
Protein kinases are enzymes that catalyze the phosphorylation of hydroxyl groups of tyrosine, serine, and threonine residues of proteins. Many aspects of cell life (for example, cell growth, differentiation, proliferation, cell cycle and survival) depend on protein kinase activities. Furthermore, abnormal protein kinase activity has been related to a host of disorders such as cancer and inflammation. Therefore, there is a great deal of effort directed to identifying ways to modulate protein kinase activities. In particular, many attempts have been made to identify small molecules which act as protein kinase inhibitors

Various quinolinone derivatives have recently been disclosed in patents such as WO 01/28993, WO 01/29025, WO 01/62251, WO 01/62252, WO 02/22598, WO 03/20699, WO 03/37252, WO 2004/087651, and WO 2004/018419. These compounds were reported as protein kinase inhibitors. The clinical utility of these compounds has been promising, but has been partially compromised due to the relatively poor aqueous solubility and/or other drug properties. What is needed is a class of modified quinolinone based derivatives having both inhibitory activity and enhanced drug properties.

Summary:

The invention is directed to quinolinone based derivatives and to their use as inhibitors of protein kinases. It is disclosed herein that hydroxy carboxy quinolinonone derivatives have enhanced and unexpected drug properties that advantageously distinguish this class of compounds over known quinolinone based derivatives having protein kinase inhibition activity. It is also disclosed herein that hydroxy carboxy quinolinone based derivatives are useful in treating disorders related to abnormal protein kinase activities such as cancer.

One aspect of the invention is directed to a compound represented by Formula (I):



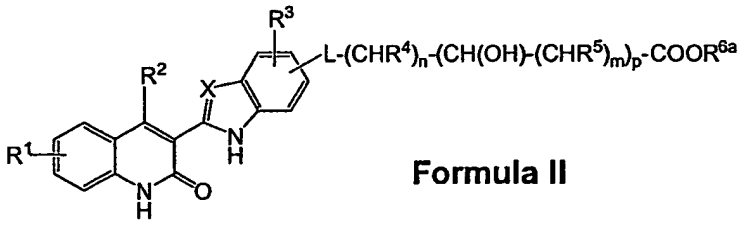
Formula I

In Formula I, R^1 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, amino, (C1-C6) alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted (C6-C10) aryl; R^2 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, alkoxy, (C1-C6) alkoxy(C1-C6) alkyl, amino, (C1-C6) alkylamino, (C6-C10) arylamino; R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, halo, cyano; R^4 is selected from the group consisting of hydrogen and (C1-C6) alkyl; R^5 is selected from the group consisting of hydrogen, (C1-C6) alkyl and hydroxyl; R^6 is selected from the group consisting of hydroxyl, O-(C1-C6) alkyl, O-(C3-C8) cycloalkyl, substituted or unsubstituted O-(C6-C10) aryl, and NR^7R^8; where R^7 and R^8 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C9) heteroaryl, (C3-C8) cycloalkyl carboxylic

acid, or R^7 and R^8 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; **n** and **m** are independently 0, 1, 2, or 3; **p** is 1, 2, or 3; X is selected from the group consisting of CR^9 and N; where R^9 is selected from the group consisting of hydrogen, halo, and (C1-C6) alkyl; L is a divalent linker selected from the group consisting of -O-, $-NR^{10}-$, $-C(O)-NR^{10}-$, $-NR^{10}-C(O)-NR^{11}-$, $-CHR^{10}-NR^{11}-$, $-CHR^{10}-NR^{11}-C(O)-NR^{12}-$, $-S(O_2)-NR^{10}-$, $-O-CHR^{10}-C(O)-NR^{11}-$, and $-CH_2-CH_2-NR^{10}-$; and R^{10}, R^{11}, and R^{12} are independently is selected from the group consisting of hydrogen and (C1-C6) alkyl. Alternatively, this aspect of the invention may also be directed to a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug of compounds represented by Formula (**I**). Key features of this aspect of the invention include the hydroxyl moiety or moieties between R^4 and R^5 and the carboxy moiety between R^5 and R^6. It is disclosed herein that these key features enhance the drug properties of the attached quinolinone pharmacophore.

As illustrated above, this first aspect of the invention may be divided into two categories. The first category includes acids and esters; the second category includes amides.

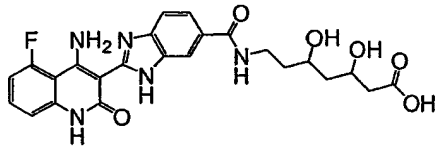
One preferred embodiment of this first category may be represented by Formula (**II**):



Formula II

In Formula II, R^{6a} is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, and substituted or unsubstituted (C6-C10) aryl. In a preferred embodiment, X is selected from the group consisting of CH and N; R^1 is selected from the group consisting of hydrogen, halo, and cyano; R^2 is selected from the group consisting of hydrogen, hydroxyl, (C1-C6)alkoxy, $-NH_2$, and $-NHR^{13}$, where

R^{13} is (C1-C6)alkyl; R^4, R^5 and R^{6a} are hydrogen; **n**, and **p** are independently 1, or 2; **m** is 0 or 1; L is selected from the group consisting of -C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{11}-, -CHR^{10}-NR^{11}-C(O)-NR^{12}-, -O-CHR^{10}-C(O)-NR^{11}-, -$S(O_2)$-NR^{10}-; where R^{10}, R^{11} and R^{12} are independently hydrogen and (C1-C6)alkyl. Preferred examples include the following: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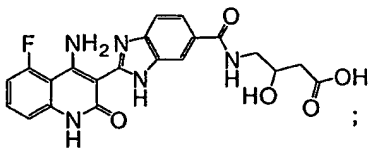
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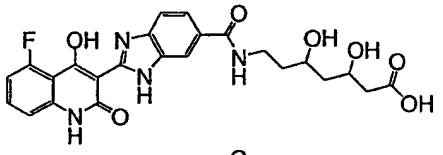
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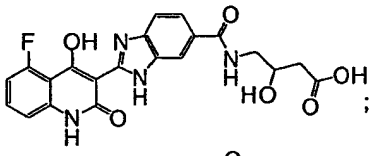
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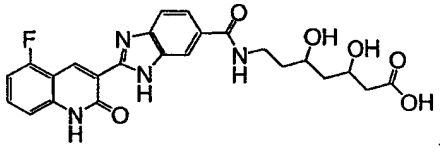
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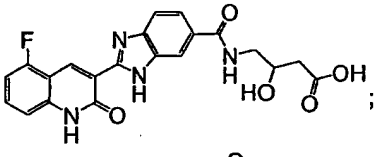
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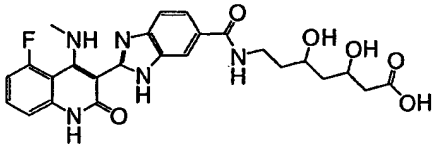
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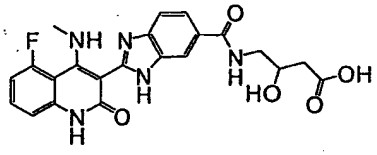
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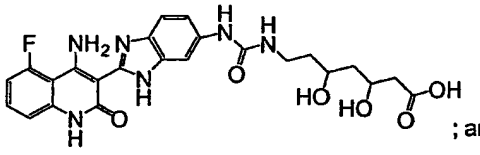
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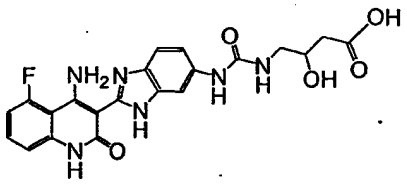

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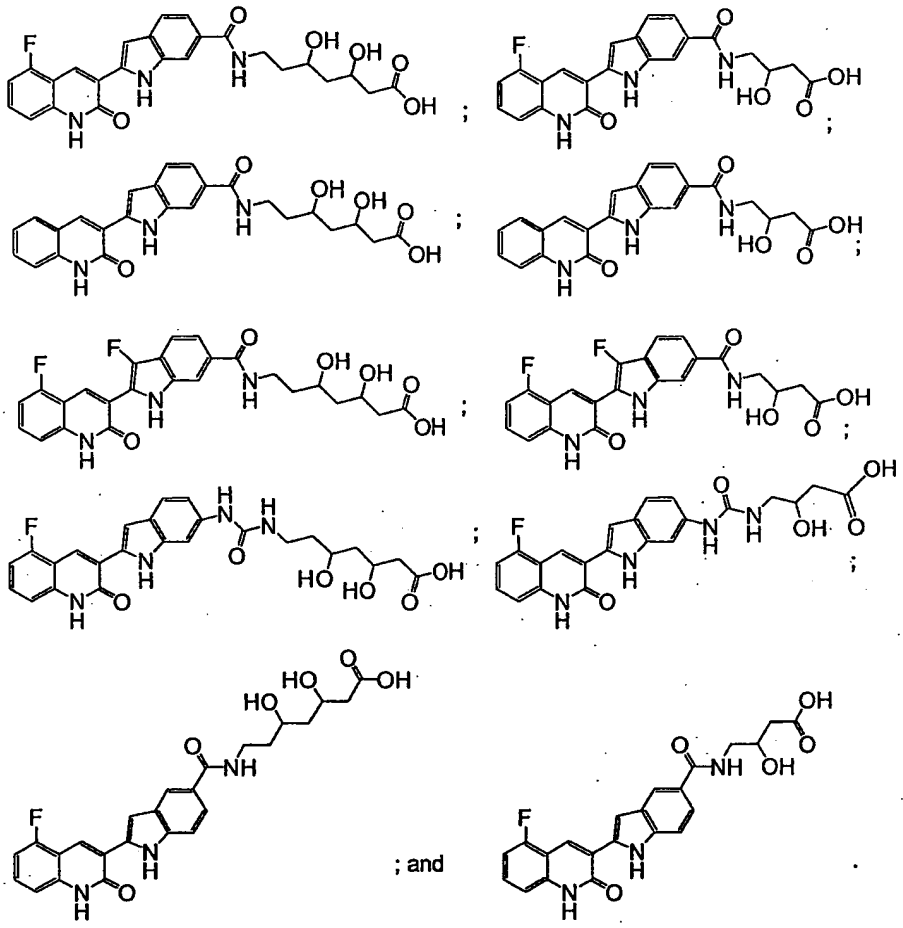

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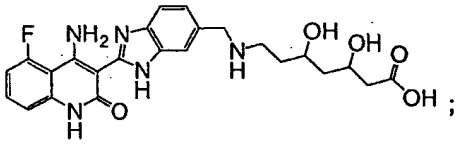
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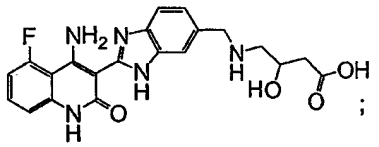
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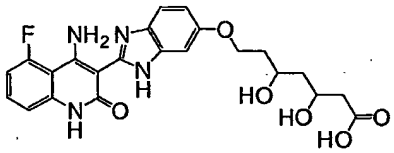
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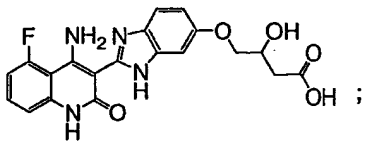
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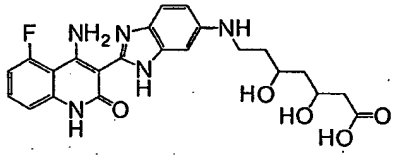
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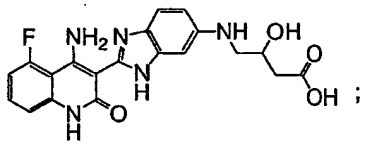
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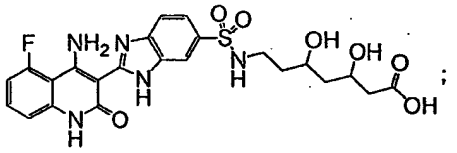
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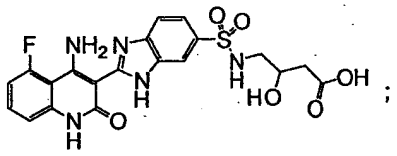
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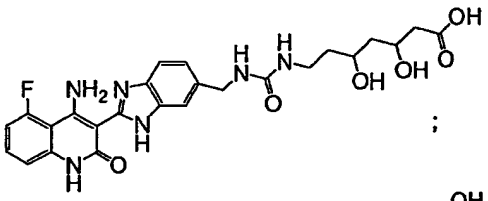
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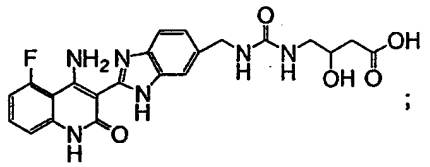
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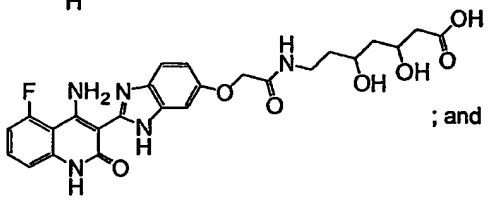
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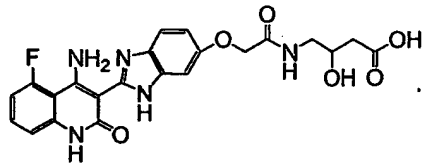
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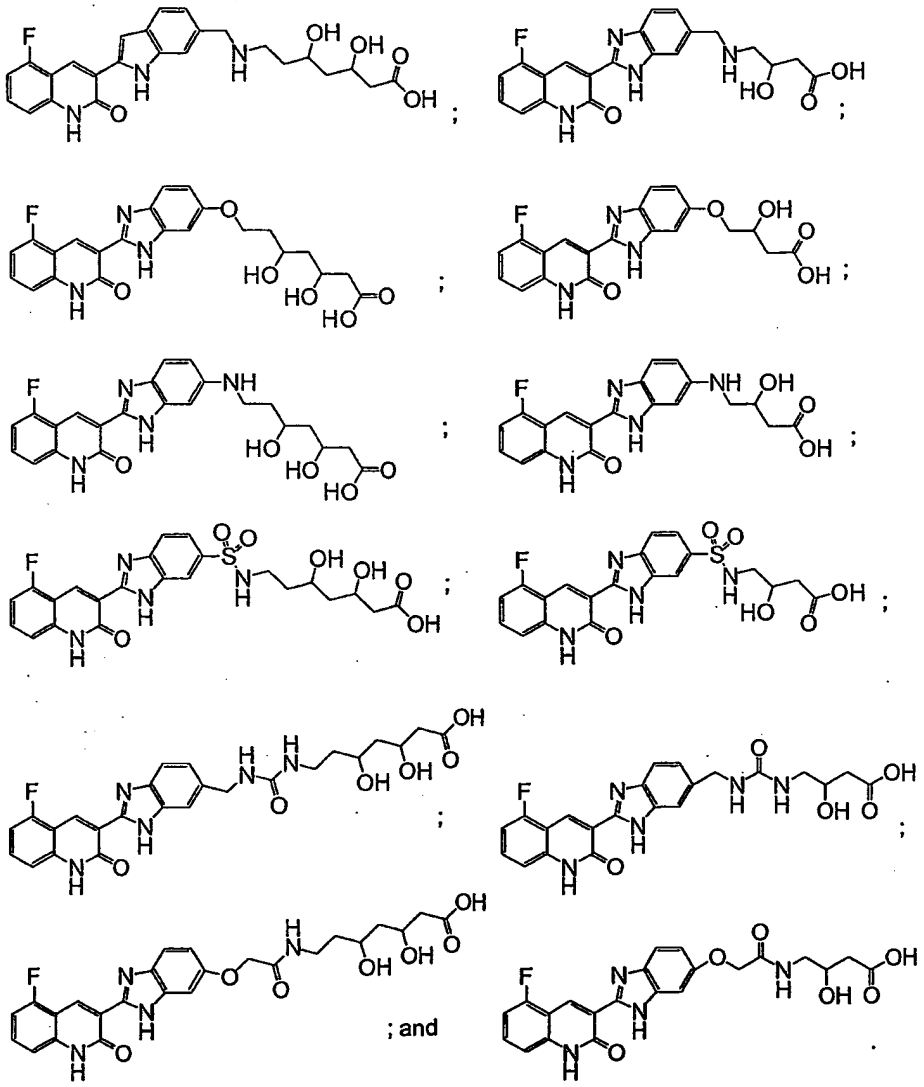
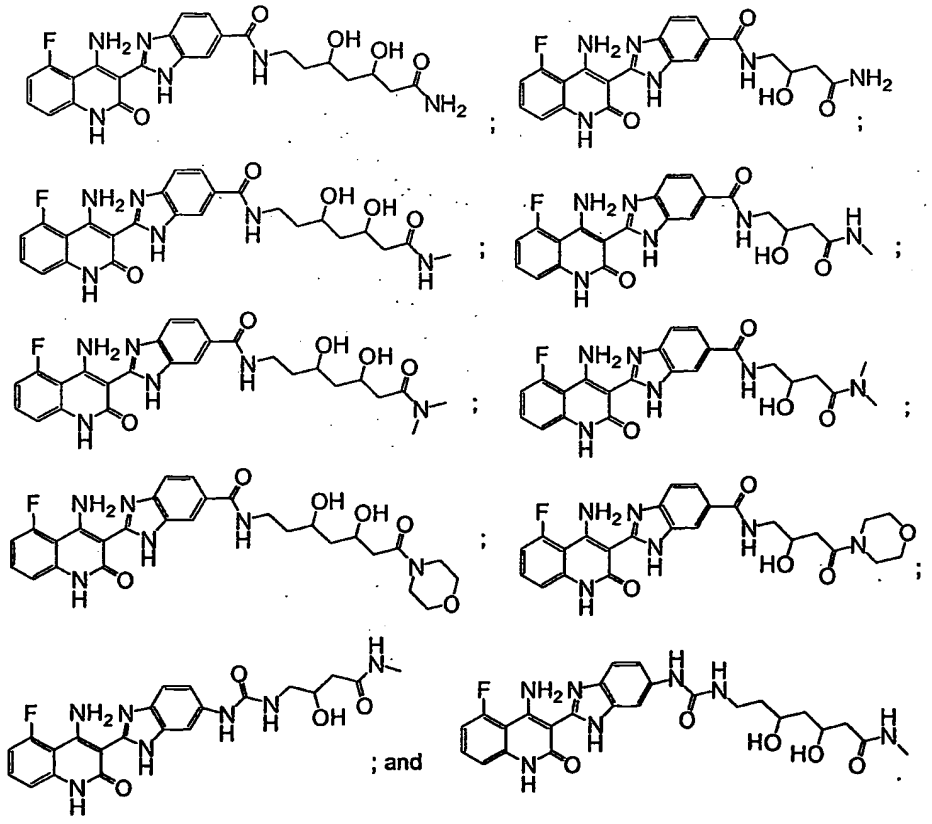


; and

The second category of the first aspect of the invention is embodied by a compound, salt, tautomer, or prodrug according to claim 1 wherein R^6 is NR^7R^8. In a preferred embodiment of this second category, X is selected from the group consisting of CH and N; R^1 is selected from the group consisting of hydrogen, halo, and cyano; R^2 is selected from the group consisting of hydrogen, hydroxyl,

(C1-C6)alkoxy, -NH_2, and -NHR^{13}, where R^{13} is (C1-C6)alkyl; R^4, R^5 and R^6 are hydrogen; **n**, and **p** are independently 1, or 2; **m** is 0 or 1; L is selected from the group consisting of -$C(O)$-NR^{10}-, -NR^{10}-$C(O)$-NR^{11}-, -CHR^{10}-NR^{11}-$C(O)$-NR^{12}-, -O-CHR^{10}-$C(O)$-NR^{11}-, -$S(O_2)$-NR^{10}-; where R^{10}, R^{11} and R^{12} are independently hydrogen and (C1-C6)alkyl; and R^7 and $R^8$are selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C8) heteroaryl, (C3-C9) cycloalkyl carboxylic acid, or $R^7$and R^8 together with N form a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids. Preferred examples include the following:



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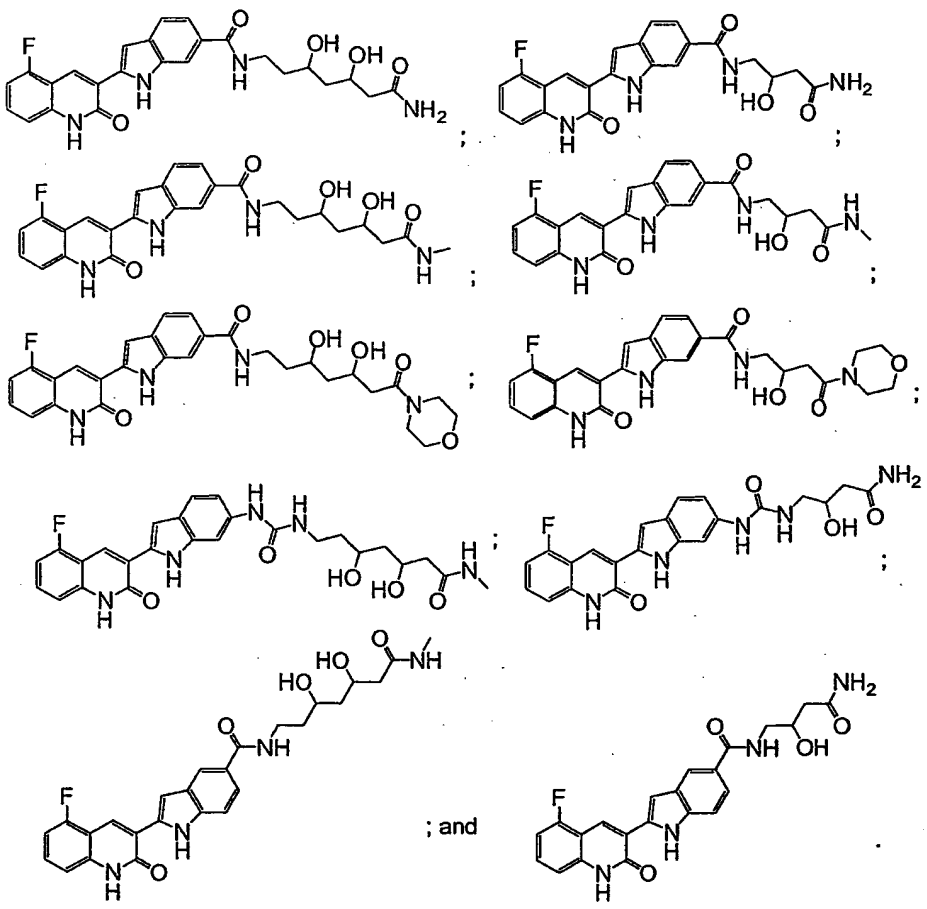

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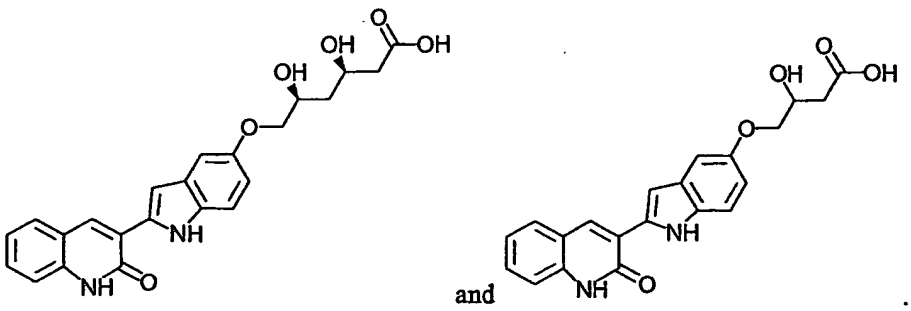
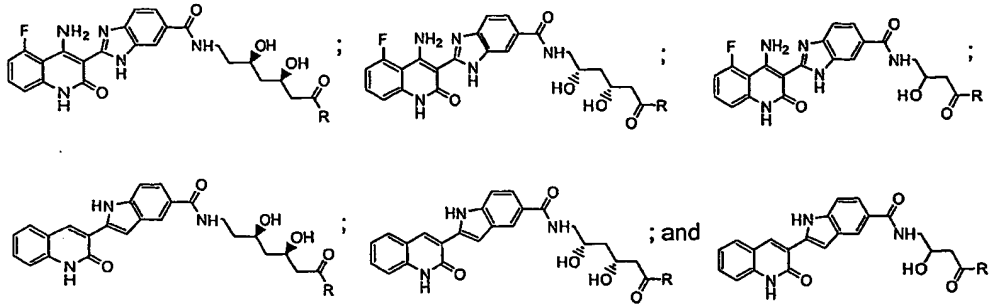
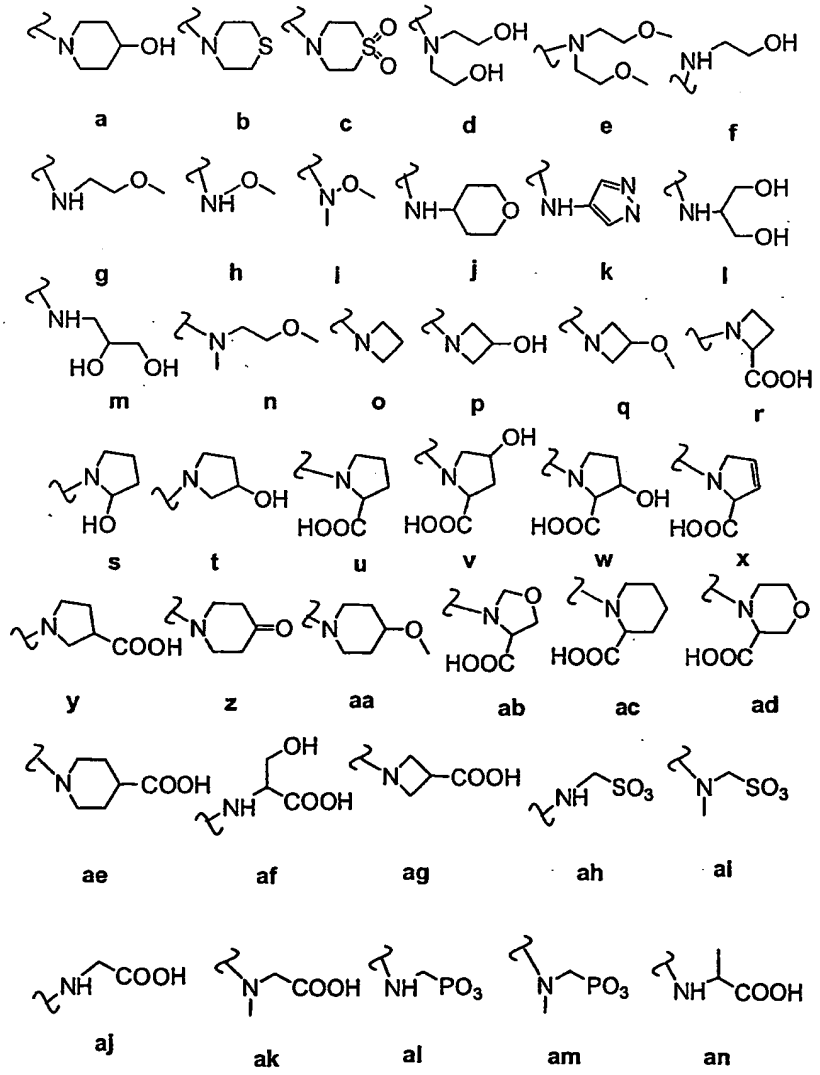


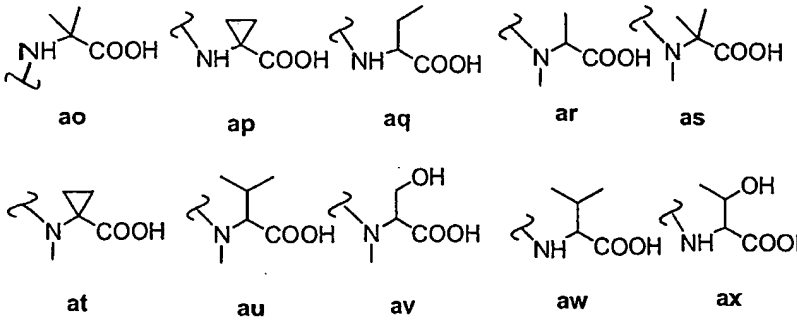
and

Other preferred examples include the following:



wherein R is selected from the group consisting of radicals represented by the following structures:





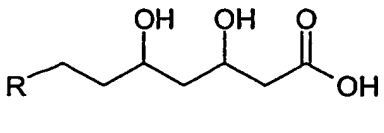
Provisios may apply to any of the above categories or embodiments wherein any one or more of the other above described embodiments or species may be excluded from such categories or embodiments.

Another aspect of the invention is directed to a method for the modulation of the catalytic activity of a protein kinase with a compound or salt of the first aspect of the invention. In a preferred mode, the protein kinase is selected from the group consisting of VEGF receptors and PDGF receptors.

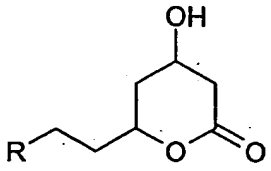
Detailed Description:

This invention discloses that hydroxy carboxy quinolinone derivatives have unexpected drug properties that advantageously distinguish them from known compounds. They are therefore useful in treating disorders related to abnormal protein kinase activities such as cancer.

It should be understood that a compound of Formula (II) may exist in its open-acid form or its cyclic-lactone form or the two forms may co-exist in solution or *in vivo* as illustrated below:



Open-acid form



Cyclic-lactone form

Furthermore, all compounds of Formula (I) have at least one asymmetric center and the stereochemistry at the asymmetric center(s) is(are) either *RS*, *R*, or *S*.

In addition, some of the compounds of Formula (I) may exhibit the phenomenon of tautomerism. As the chemical structures shown in the present invention can only represent one of the possible tautomeric forms, it should be understood that the invention encompasses any tautomeric form of the drawn structure. For example, any claim to compound **A** below is understood to include tautomeric structure **B**, and vice versa, as well as mixtures thereof.

A **B**

Tautomerism may also result from limited rotation about a chemical single bond if there is steric hindrance and/or intra-molecular hydrogen bonding that limits the otherwise free rotation about that bond. It should be understood that the invention also encompasses any rotomers of the drawn structure.

Utility

The present invention provides compounds capable of regulating and/or modulating protein kinase activities of, but not limited to, VEGFR (Vascular Endothelial Growth Factor Receptor) and/or PDGFR (Platelet-Derived Growth Factor Receptor). Thus, the present invention provides a therapeutic approach to the treatment of disorders related to the abnormal functioning of these kinases. Such disorders include, but not limited to, solid tumors such as glioblastoma, melanoma, and Kaposi's sarcoma, and ovarian, lung, prostate, pancreatic, colon and epidermoid carcinoma. In addition, VEGFR/PDGFR inhibitors may also be used in the treatment of restenosis and diabetic retinopathy.

Furthermore, this invention relates to the inhibition of vasculogenesis and angiogenesis by receptor-mediated pathways, including the pathways comprising VEGF receptors, and/or PDGF receptors. Thus the present

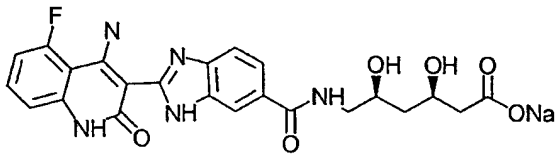
invention provides therapeutic approaches to the treatment of cancer and other diseases which involve the uncontrolled formation of blood vessels.

Synthesis of Acid Compounds

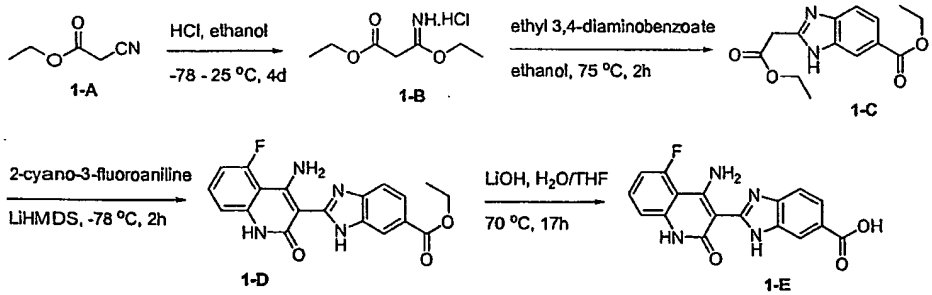
The compounds of this invention can be synthesized by following the published general procedures disclosed in WO 01/28993, WO 01/29025, WO 01/62251, WO 01/62252, WO 02/22598, WO 03/20699, WO 03/37252, WO 2004/087651, and WO 2004/018419 and in Kuethe et al. Org. Lett. (2003), 5(21), 3975; Manley et al. Org. Lett. (2004), 6(14), 2433; and Kumar et al. Org. Lett. (2004), 6(1), 7. But the following intermediates are specific to compounds of this invention and may be used in place of their respective counterparts in the published general procedures: (4*R*,6*R*)-*t*-butyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, *t*-Butyl(3*R*,5*S*)-6-hydroxy-3,5-O-isopropylidene-3,5-dihydroxyhexanoate, and 4-amino-3-hydroxy-butanoic acid. These intermediates may be purchased from commercial sources (e.g. Fisher Scientific, Fairlawn, New Jersey, or Kaneka Corp., Japan). Another variation from the published general procedures is that in the synthesis of compounds using (4*R*,6*R*)-*t*-butyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, the protecting groups need to be removed from the final product. These variations from the published general procedures can be understood and carried out by those skilled in the art. Thus, the compounds of the present invention can be synthesized by those skilled in the art.

The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

Example 1: (3*R*,5*S*)-6-{[2-(4-Amino-5-fluoro-2-oxo-1,2-dihydro-quinolin-3-yl)-3H-benzoimidazole-5-carbonyl]-amino}-3,5-dihydroxy-hexanoic acid, sodium salt.



The preparation of the title compound was accomplished by first synthesizing compound **1-E** as shown in Scheme 1 below:



Scheme 1

*Preparation of compound **1-B**.* HCl in dioxane (4M, 25 mL, 100 mmol) was added to a solution of compound **1-A** (50 mmol) in anhydrous ethanol (60 mmol) at -30 °C under argon. After stirring at -30 °C for 4h, the solution was sitting at 0 °C for 4d. Then, the solution was stirred at room temperature. During this stirring, precipitation was observed. The solvents were filtrered off, and the solid was washed twice using *tert*-butylmethyl ether. This solid was dried under high vacuum to obtain the final product **1-B** (9.3g, 94%). This compound was used directly in the following steps without further characterization.

*Prepratation of compound **1-C**.* Anhydrous THF (30 mL) and anhydrous ethanol (30 mL) were added to a flask charged with compound **1-B** (2.5g, 13 mmol), and ethyl 3, 4-diaminobenzoate (1.96g, 11 mmol) under argon. After stirring at 0 °C for 1h, the solution was continuously stirred at 25 °C overnight, and LC-MS showed a complete reaction. The solvents were removed via evaporation under reduced pressure, and the resulting residue was suspended in ethyl acetate (250 mL). This solution was washed using saturated $NaHCO_3$ (3x) and brine (3x), dried over Na_2SO_4, and evaporated under vacuum to get the crude product. This crude material was subjected to flash chromatography

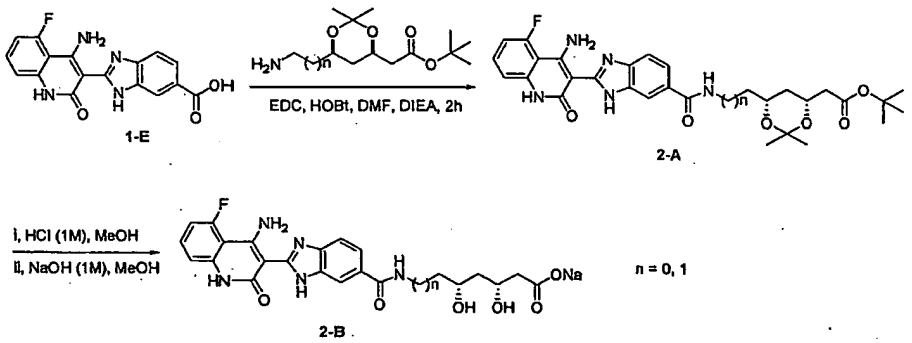
(ISCO system, 1% – 5% MeOH in DCM, 22 min.) to obtain the final product **1-C** (2.85g, 95%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{14}H_{16}N_2O_4$: 277, obtained: 277. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 12.73 (d, *J* = 12 Hz, 1H), 8.12 (d, *J* = 28 Hz, 1H), 7.80 (dd, *J* = 8.8 Hz, *J* = 16 Hz, 1H), 7.60 (dd, *J* = 8.4 Hz, *J* = 28 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.02 (s, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H).

*Preparation of compound **1-D**.* LiHMDS in THF (1.0M, 20 mL) was added to a solution of compound **1-C** (2.28g, 8.24 mmol) in anhydrous THF (20 mL) under argon. After stirring at -78 °C for 1h, 2-Cyano-3-fluoroaniline (1.2g, 8.8 mmol, dissolved in THF) was added. The solution was warmed up to 25 °C, and stirred at this temperature for another 1h. The solvent was removed via evaporation under reduced pressure, and the resulting residue was suspended in ethyl acetate (150 mL). This solution was washed using brine (3x), dried over Na_2SO_4, and evaporated under vacuum to get the crude product. This crude material was subjected to flash chromatography (ISCO system, 1% – 5% MeOH in DCM, 22 min.) to obtain the final product **1-D** (2.3g, 76%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{19}H_{15}FN_4O_3$: 367, obtained: 367. ^{1}H–NMR (DMSO-d_6, 400 MHz), δ 12.80 (s, 1H), 11.12 (s, 1H), 8.18 (b, 1H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.77 (dd, *J* = 1.6 Hz, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.61 (b, 1H), 7.31 (t, *J* = 8.8 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.17 (s, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

*Preparation of compound **1-E**.* LiOH (21 mmol) in H_2O (10 mL) was added to a solution of compound **1-D** (1.22g, 3.33 mmol) in THF (20 mL). The solution was heated to and stirred at 70 °C overnight. The THF was removed via evaporation under reduced pressure, and the resulting aqueous solution was acidified to pH ~3 using concentrated HCl. A precipitate was formed, and the precipitation was collected by filtration, and washed using H_2O several times. The resulting solid was dried under high vacuum to give the final product **1-E** (0.45g, 40%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{17}H_{11}FN_4O_3$: 339, obtained: 339. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.20 (s, 1H), δ 12.70 (s, 1H), 11.62 (s, 1H), 11.32 (s, 1H), 8.27 (b, 1H), 7.93 (d, *J* = 13.6 Hz, 1H), 7.81

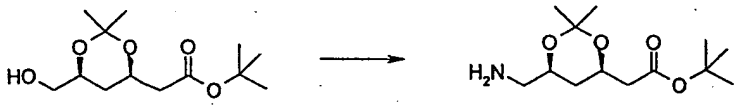
(dd, J = 1.2 Hz, J = 8.0 Hz, 1H), 7.70 (b, 2H), 7.57 (dd, J = 1.6 Hz, J = 8.4 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.0 Hz, J = 14.0 Hz, 1H).

Compound **1-E** was converted to the title compound as shown in Scheme 2 below:



Scheme 2

Preparation of ((4*R*,6*S*)-6-Aminomethyl-2,2-dimethyl-[1,3]dioxan-4-yl)-acetic acid tert-butyl ester:



Triflic anhydride 1.4mL (2.36g, 8.345mmol) was dropwise added at -78 °C to a solution of 2,6-lutidine 1.35mL (11.63mmol) and t-Butyl(3R,5S)-6-hydroxy-3,5-O-isopropylidene-3,5-dihydroxyhexanoate 1.981g (7.609 mmol, obtained from Kaneka Corp.) in dichloromethane (anh., 50mL) over 3 minutes. The mixture was stirred at -78 °C for 10 min, then placed on ice-slush bath and stirred at 0 °C for 45 min. The resulting pink mixture was transferred into ice-cooled solution of ammonia in methanol (7M solution, 200mL). The mixture was placed on ambient water bath and stirred at RT for 6 hours. The reaction mix was evaporated to dryness, the residue partitioned between ether (200mL) and aqueous potassium carbonate (6g in 200 mL of water), the aqueous phase re-extracted with ether (150mL). Combined organic extracts were dried (magnesium sulfate) and evaporated. The crude product was purified on a

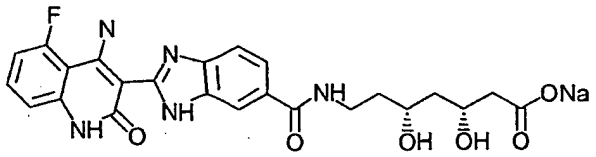
column of silica (125g) eluting with a mix chloroform-methanol-conc. aq. ammonia 100:10:1 (v/v) (1.5L)
Y = 1.777g of a colorless liquid (90% th)
^{1}H (^{d}DMSO, 400MHz): 4.167(m, 1H), 3.741 (m, 1H), 2.484 (m, 2H), 2.384 (ddAB, J=15.2Hz, 5.1Hz, 1H), 2.201(ddAB, J=15Hz, 7.8Hz, 1H), 1.533 (br d, J=12.5Hz, 1H), 1.373 (s, 9H), 1.363 (s, 3H), 1.250 (br s, 2H), 1.223 (s, 3H)

*Preparation of compound **2-A (n=0).*** The amine prepared above (0.1g, 0.39 mmol) was added to a solution of compound **1-E** (0.1g, 0.3 mmol), EDC (0.4 mmol), HOBt (0.4 mmol), and DIEA (1 mmol) in DMF (2 mL). After the solution was stirred at 25 °C for 2h, DMF was removed via evaporation under reduced pressure. The resulting residue was suspended in ethyl acetate (100 mL), washed by saturated $NaHCO_3$ (3x) and brine (3x), and dried over Na_2SO_4. The ethyl acetate was removed under reduced pressure to give the crude product. This crude material was subjected to flash chromatography (ISCO system, 1% – 6% MeOH in DCM, 22 min.) to obtain the final product **2-A** (145mg, 85%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{30}H_{34}FN_5O_6$: 580, obtained: 580. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.10 (d, *J* = 7.2 Hz, 1H), 11.64 (d, *J* = 4.0 Hz, 1H), 11.35 (s, 1H), 8.45 (dt, *J* = 6.0 Hz, *J* = 29.2 Hz, 1H), 8.18 (d, *J* = 12.0 Hz, 1H), 7.92 (t, *J* = 12.0 Hz, 1H), 7.72 (m, 1H), 7.68 (m, 1H), 7.58 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.05 (dd, *J* = 8.0 Hz, *J* = 14.0 Hz, 1H), 4.19 (m, 1H), 4.09 (m, 1H), 3.57 (t, *J* = 6.0 Hz, 1H), 3.24 (m, buried in water signal, 1H), 2.40 (dd, *J* = 4.4 Hz, *J* = 15.2 Hz, 1H), 2.22 (dd, *J* = 8.0 Hz, *J* = 15.2 Hz, 1H), 1.65 (m, 1H), 1.40 (s, 3H), 1.37 (s, 9H), 1.28 (s, 3H), 1.10 (m, 1H).

*Preparation of compound **2-B (n=0).*** Aqueous HCl (4 mL, 1.0M) was added to a solution of compound **2-A** (215 mg, 0.36 mmol) in MeOH (4 mL). A precipitation was observed immediately. After the suspension was stirred at 50 °C for 2.5h, the solution became clear, and LC-MS showed the reaction to remove the acetonide protection group was complete. The solvent was removed via evaporation under reduced pressure. The resulting crude material was used directly in the next step without further purification. Thus, the aqueous NaOH (5 mL, 1.0M) was added to a solution of this crude material in

MeOH (7 mL). The solution was stirred at 25 °C for 1h, and LC-MS showed the reaction to remove the *t*-butyl ester was complete. This solution was directly subjected to preparative HPLC to obtain the final title compound (130 mg, 72%). LC-MS: single peak at 254 nm, MH^+ calcd. for the acid $C_{23}H_{22}FN_5O_6$: 484, obtained: 484. ^{1}HNMR (CD_3OD, 400 MHz), δ 8.12 (s, 1H), 7.73 (dd, *J* = 2.0 Hz, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.54 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.98 (dd, *J* = 8.0 Hz, *J* = 14.4 Hz, 1H), 4.19 (m, 1H), 4.05 (m, 1H), 3.55 (dd, *J* = 5.2 Hz, *J* = 13.2 Hz, 1H), 3.46 (dd, *J* = 6.8 Hz, *J* = 13.2 Hz, 1H), 2.41 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H), 2.32 (dd, *J* = 8.0 Hz, *J* = 15.4 Hz, 1H), 1.73 (m, 2H).

Example 2: (3*R*,5*R*)-7-{[2-(4-Amino-5-fluoro-2-oxo-1,2-dihydro-quinolin-3-yl)-3H-benzoimidazole-5-carbonyl]-amino}-3,5-dihydroxy-heptanoic acid, sodium salt.



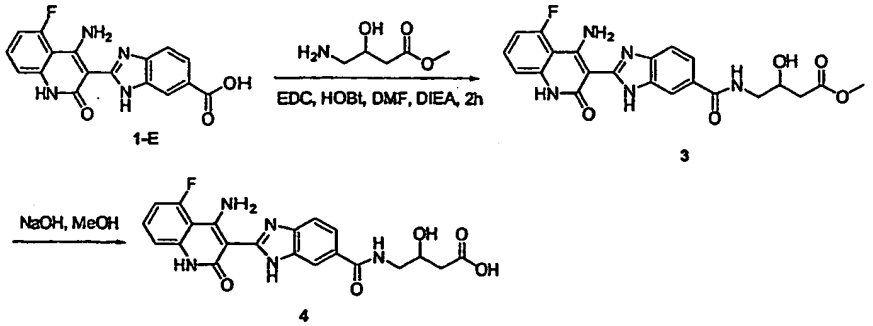
The preparation of the title compound was carried out following the procedure for Example 1.

Preparation of compound ***2-A (n=1).*** The amine (0.15g, 0.55 mmol) was added to a solution of compound **1-E** (0.14g, 0.41 mmol), EDC (0.6 mmol), HOBt (0.6 mmol), and DIEA (1 mmol) in DMF (2 mL). After the solution was stirred at 25 °C for 2h, DMF was removed via evaporation under reduced pressure. The resulting residue was suspended in ethyl acetate (150 mL), washed by saturated $NaHCO_3$ (3x) and brine (3x), and dried over Na_2SO4. The ethyl acetate was removed under reduced pressure to give the crude product. This crude material was subjected to flash chromatography (ISCO system, 1% – 5% MeOH in DCM, 22 min.) to obtain the product **2-A** (170mg, 69%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{31}H_{36}FN_5O_6$: 594, obtained: 594. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.09 (d, *J* = 6.4 Hz, 1H), 11.64 (d, *J* = 5.2 Hz, 1H), 11.35 (s, 1H), 8.35 (m, 1H), 8.16 (d, *J* = 14.0 Hz, 1H), 7.92 (t, *J* = 12.8 Hz,

1H), 7.72 (m, 1H), 7.64 (m, 1H), 7.57 (m, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.05 (dd, J = 8.0 Hz, J = 14.0 Hz, 1H), 4.20 (m, 1H), 4.00 (m, 1H), 3.59 (t, J = 5.6 Hz, 1H), 3.30 (m, buried in water signal, 1H), 2.38 (dd, J = 4.8 Hz, J = 15.2 Hz, 1H), 2.22 (dd, J = 8.0 Hz, J = 14.8 Hz, 1H), 1.60 (m, 3H), 1.40 (s, 3H), 1.38 (s, 9H), 1.25 (s, 3H), 1.10 (dd, J = 12.0 Hz, J = 24.0 Hz, 1H).

Preparation of compound ***2-B (n=1)***. Aqueous HCl (4 mL, 1.0M) was added to a solution of compound **2-A** (157 mg, 0.27 mmol) in MeOH (4 mL). A precipitation was observed immediately. After the suspension was stirred at 50 °C for 0.5h, the solution became clear, and LC-MS showed the reaction to remove the acetonide protection group was complete. The solvent was removed via evaporation under reduced pressure. The resulting crude material was used directly in the next step without further purification. Thus, the aqueous NaOH (5 mL, 1.0M) was added to a solution of this crude material in MeOH (7 mL). The solution was stirred at 25 °C for 1h, and LC-MS showed the reaction to remove the *t*-butyl ester was complete. This solution was directly subjected to preparative HPLC to obtain the final title compound (135 mg, 96%). LC-MS: single peak at 254 nm, MH^+ calcd. for the acid $C_{24}H_{24}FN_5O_6$: 496, obtained: 496. ^{1}HNMR (CD_3OD, 400 MHz), δ 8.10 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.52 (m, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.97 (dd, J = 8.0 Hz, J = 13.2 Hz, 1H), 4.16 (m, 1H), 3.95 (m, 1H), 3.60 (m, 1H), 3.53 (m, 1H), 2.35 (m, 2H), 1.88 (m, 2H), 1.72 (m, 2H).

Examples 3 and 4. The preparation of Examples **3** and **4** followed Scheme 3 shown below:



Scheme 3

Preparation of Example 3. Methyl 4-amino-3-hydroxylbutyrate (0.1g, 0.7 mmol) was added to a solution of compound **1-E** (0.18g, 0.53 mmol), EDC (1 mmol), HOBt (1 mmol), and DIEA (2 mmol) in DMF (4 mL). After the solution was stirred at 25 °C for 1h, DMF was removed via evaporation under reduced pressure. The resulting residue was suspended in ethyl acetate (100 mL), washed by saturated $NaHCO_3$ (3x) and brine (3x), and dried over Na_2SO_4. The ethyl acetate was removed under reduced pressure to give 240 mg crude product. A portion (60 mg) of this crude material was subjected to preparative HPLC to obtain the final product, 4-{[2-(4-Amino-5-fluoro-2-oxo-1,2-dihydro-quinolin-3-yl)-3H-benzoimidazole-5-carbonyl]-amino}-3-hydroxy-butyric acid methyl ester (15mg, 85%). LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{22}H_{20}FN_5O_5$: 454, obtained: 454. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.11 (s, 1H), 11.63 (s, 1H), 11.35 (s, 1H), 8.41 (dt, *J* = 5.6 Hz, *J* = 25.6 Hz, 1H), 8.20 (d, *J* = 10.8 Hz, 1H), 7.91 (t, *J* = 13.2 Hz, 1H), 7.73 (s, 1H), 7.60 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.05 (dd, *J* = 8.0 Hz, *J* = 14.0 Hz, 1H), 5.13 (d, *J* = 5.6 Hz, 1H), 4.09 (m, 1H), 3.57 (s, 3H), 3.29 (m, buried in water signal, 2H), 2.56 (dd, *J* = 4.4 Hz, *J* = 16.0 Hz, 1H), 2.31 (dd, *J* = 9.2 Hz, *J* = 14.4 Hz, 1H).

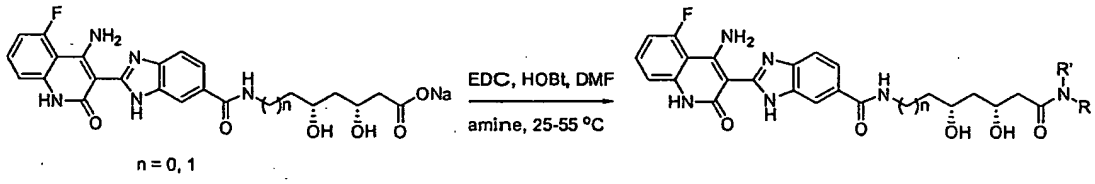
Preparation of Example 4. LiOH (1 mmol) in H_2O (10 mL) was added to a solution of compound ***3*** (180 mg, 0.4 mmol) in MeOH (10 mL). After the suspension was stirred at 25 °C overnight, the MeOH was removed via evaporation under reduced pressure. The resulting aqueous solution was directly subjected to preparative HPLC to obtain the final pure product **4**, 4-{[2-(4-Amino-5-fluoro-2-oxo-1,2-dihydro-quinolin-3-yl)-3H-benzoimidazole-5-carbonyl]-amino}-3-hydroxy-butyric acid (135 mg, 96%). LC-MS: single peak at 254 nm, MH^+ calcd. for the acid $C_{21}H_{18}FN_5O_5$: 440, obtained: 440. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.05 (s, 1H), 11.35 (s, 1H), 8.60 (dt, *J* = 5.6 Hz, *J* = 60.0 Hz, 1H), 8.50 (s, 1H), 8.19 (d, *J* = 16.8 Hz, 1H), 7.90 (t, *J* = 12.0 Hz, 1H), 7.72 (s, 1H), 7.64 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.04 (dd, *J* = 8.0 Hz, *J* = 13.6 Hz, 1H), 3.84 (m, 1H), 3.24 (m, buried in water signal, 2H), 2.16 (m, 1H), 1.97 (m, 1H).

Synthesis of Amide Compounds

The amide compounds of this invention can be readily synthesized by those skilled in the art starting from the acid compound disclosed herein.

The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

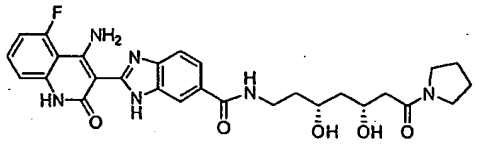
Examples 5 and 6. The preparation of Examples **5** and **6** followed Scheme **4** shown below:



Scheme 4

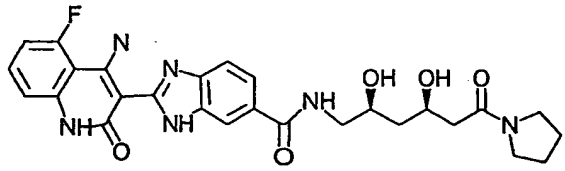
An amine (3 equiv) was added to a solution of the sodium salt of a free acid (1 equiv), EDC (5 equiv), HOBt (5 equiv), and DIEA (5 equiv) in DMF. After the solution was stirred at 25 °C overnight (stirred at 55 °C for a couple of hours if necessary), DMF was removed via evaporation under reduced pressure. The resulting residue was suspended in ethyl acetate, washed by saturated $NaHCO_3$ (3x) and brine (3x), and dried over Na_2SO_4. The ethyl acetate was removed under vacuum to give the crude product. This crude material was subjected to preparative HPLC to give the final product amide, which was subsequently characterized by LC-MS and NMR spectroscopy.

Example 5: 2-(4-Amino-5-fluoro-2-oxo-1,2-dihydro-quinolin-3-yl)-3H-benzoimidazole-5-carboxylic acid ((3*R*,5*R*)-3,5-dihydroxy-7-oxo-7-pyrrolidin-1-yl-heptyl)-amide



An amount of 86 mg (90%) product was obtained after preparative HPLC from 90 mg (0.173 mmol) of the free acid sodium salt. LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{28}H_{31}FN_6O_6$: 551, obtained: 551. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 13.40 (s, 1H), 11.25 (s, 1H), 8.39 (s, 1H), 8.16 (s, 1H), 7.85 (m, 1H), 7.69 (s, 2H), 7.55 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 8.4 Hz, J = 13.2 Hz, 1H), 4.76 (s, 1H), 4.72 (s, 1H), 4.05 (m, 1H), 3.71 (m, 1H), 3.39 (m, 2H), 3.22 (m, 2H), 3.17 (m, 2H), 2.34 (m, 2H), 1.81 (m, 2H), 1.72 (m, 4H), 1.53 (m, 2H).

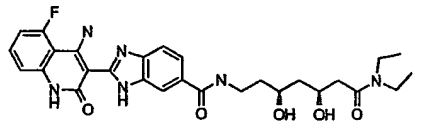
Example 6: 2-(4-Amino-5-fluoro-2-oxo-1,2-dihydro-quinolin-3-yl)-3H-benzoimidazole-5-carboxylic acid ((2*S*,4*R*)-2,4-dihydroxy-6-oxo-6-pyrrolidin-1-yl-hexyl)-amide



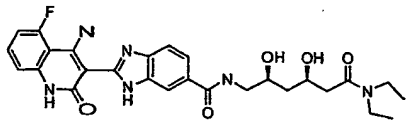
An amount of 33 mg (89%) product was obtained after preparative HPLC from 35 mg (0.069 mmol) of the free acid sodium salt. LC-MS: single peak at 254 nm, MH^+ calcd. for $C_{27}H_{29}FN_6O_6$: 537, obtained: 537. ^{1}H-NMR (DMSO-d_6, 400 MHz), δ 11.20 (s, 1H), 8.30 (s, 1H), 8.18 (s, 1H), 7.80 - 7.60 (m, 3H), 7.52 (m, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.99 (dd, J = 8.0 Hz, J = 13.2 Hz, 1H), 4.95 (s, 1H), 4.78 (s, 1H), 4.09 (m, 1H), 3.81 (m, 1H), 3.40 (m, 2H), 3.26 (m, 2H), 3.11 (m, 2H), 2.35 (m, 2H), 1.82 (m, 2H), 1.72 (m, 2H), 1.61 (m, 2H).

Example 7. Further amide derivatives of Examples 1 and 2.

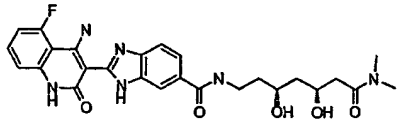
Following the above procedures or other known procedures, the following amides can be made.



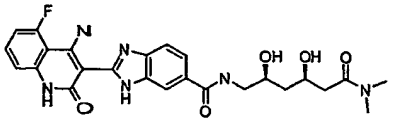
7a



7b



7c



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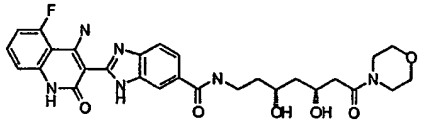
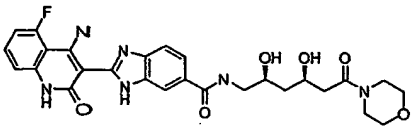


7e



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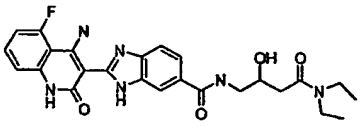
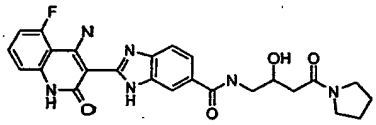
Example 8. Amide derivatives of Example 4.

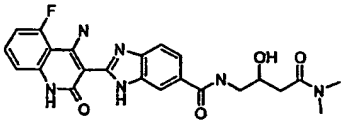
Following known procedures, the following amide derivatives of Example 4 can be made by those skilled in the art.



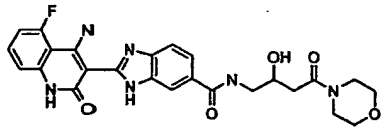
8a



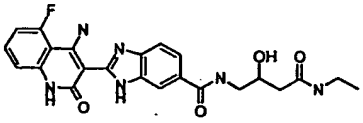
8b



8c



8d



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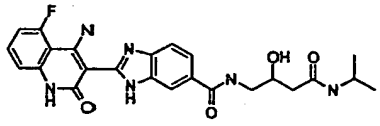
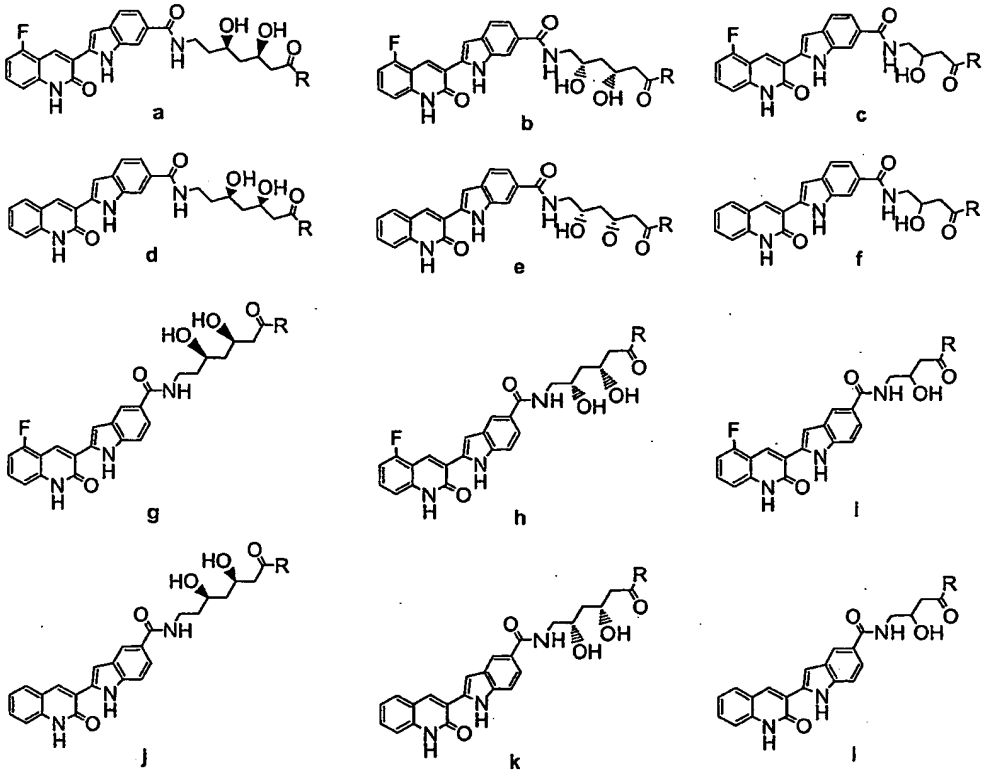


8f

Examples 9-15: Examples **9-15** are illustrated by the general structures below.



Example 9: Compounds **9a-l** where R=OH can be made by those skilled in the art based on known procedures.

Example 10: Compounds **10a-l** where R=diethylamine can be made by those skilled in the art based on known procedures.

Examples 11: Compounds **11a-l** where R=dimethylamine can be made by those skilled in the art based on known procedures.

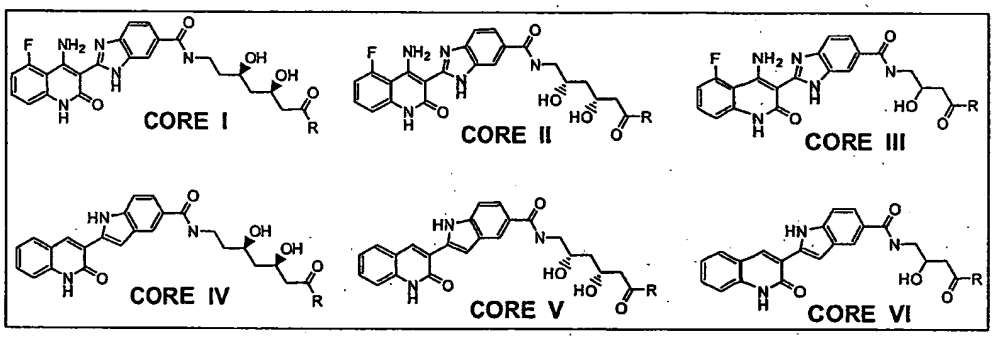
Examples 12: Compounds **12a-l** where R=pyrrolidine can be made by those skilled in the art based on known procedures.

Examples 13: Compounds **13a-l** where R=morpholine can be made by those skilled in the art based on known procedures.

Examples 14: Compounds **14a-l** where R=ethylamine can be made by those skilled in the art based on known procedures.

Examples 15: Compounds **15a-l** where R=cyclopropylamine can be made by those skilled in the art based on known procedures.

Examples 16 – 315: Still further amide examples are shown in the following table:



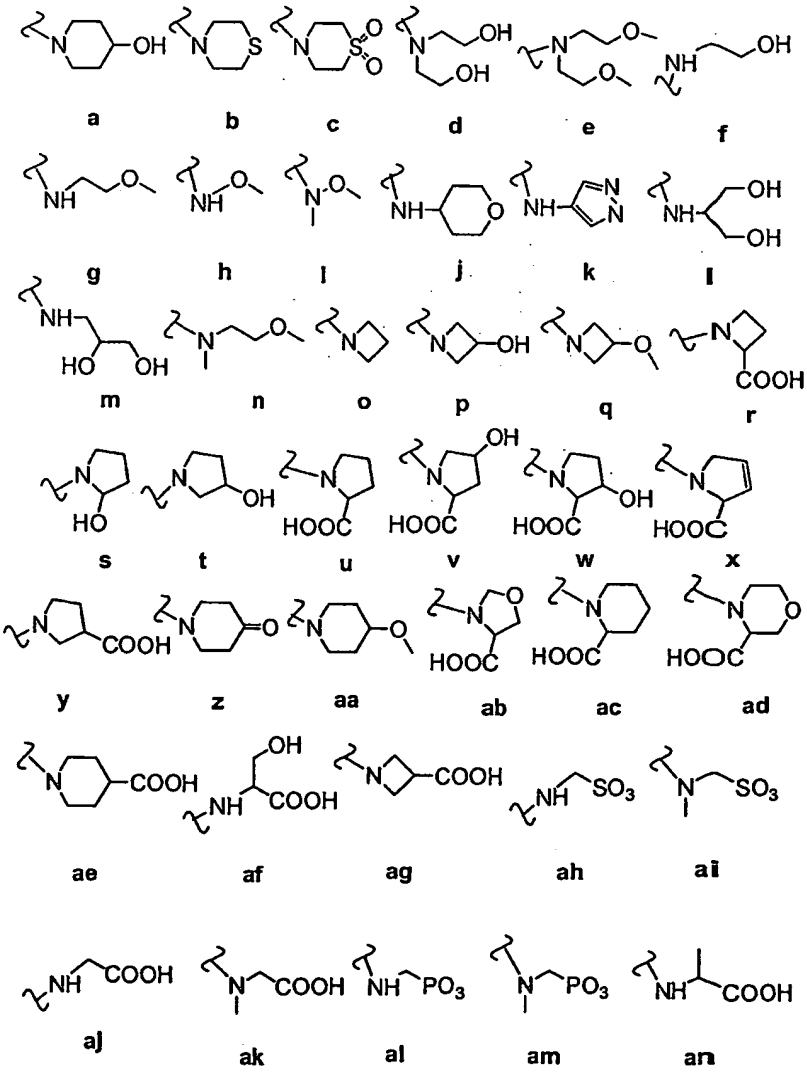
Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
16	I	a	66	II	a	116	III	a
17	I	b	67	II	b	117	III	b
18	I	c	68	II	c	118	III	c
19	I	d	69	II	d	119	III	d
20	I	e	70	II	e	120	III	e
21	I	f	71	II	f	121	III	f
22	I	g	72	II	g	122	III	g
23	I	h	73	II	h	123	III	h
24	I	i	74	II	i	124	III	i
25	I	j	75	II	j	125	III	j
26	I	k	76	II	k	126	III	k
27	I	l	77	II	l	127	III	l
28	I	m	78	II	m	128	III	m
29	I	n	79	II	n	129	III	n
30	I	o	80	II	o	130	III	o

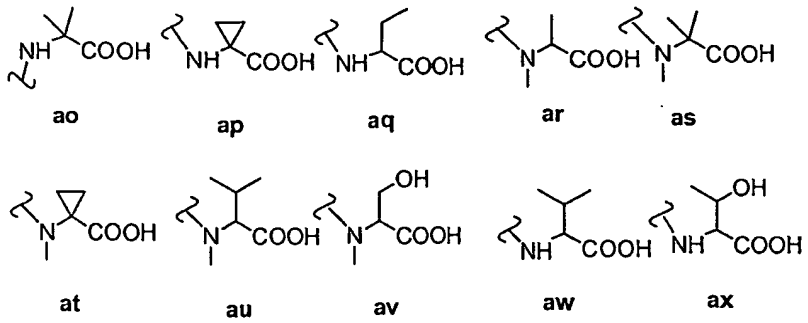
Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
31	I	p	81	II	p	131	III	p
32	I	q	82	II	q	132	III	q
33	I	r	83	II	r	133	III	r
34	I	s	84	II	s	134	III	s
35	I	t	85	II	t	135	III	t
36	I	u	86	II	u	136	III	u
37	I	v	87	II	v	137	III	v
38	I	w	88	II	w	138	III	w
39	I	x	89	II	x	139	III	x
40	I	y	90	II	y	140	III	y
41	I	z	91	II	z	141	III	z
42	I	aa	92	II	aa	142	III	aa
43	I	ab	93	II	ab	143	III	ab
44	I	ac	94	II	ac	144	III	ac
45	I	ad	95	II	ad	145	III	ad
46	I	ae	96	II	ae	146	III	ae
47	I	af	97	II	af	147	III	af
48	I	ag	98	II	ag	148	III	ag
49	I	ah	99	II	ah	149	III	ah
50	I	ai	100	II	ai	150	III	ai
51	I	aj	101	II	aj	151	III	aj
52	I	ak	102	II	ak	152	III	ak
53	I	al	103	II	al	153	III	al
54	I	am	104	II	am	154	III	am
55	I	an	105	II	an	155	III	an
56	I	ao	106	II	ao	156	III	ao
57	I	ap	107	II	ap	157	III	ap
58	I	aq	108	II	aq	158	III	aq
59	I	ar	109	II	ar	159	III	ar
60	I	as	110	II	as	160	III	as
61	I	at	111	II	at	161	III	at
62	I	au	112	II	au	162	III	au
63	I	av	113	II	av	163	III	av
64	I	aw	114	II	aw	164	III	aw
65	I	ax	115	II	ax	165	III	ax

Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
166	IV	a	216	V	a	266	VI	a
167	IV	b	217	V	b	267	VI	b
168	IV	c	218	V	c	268	VI	c
169	IV	d	219	V	d	269	VI	d
170	IV	e	220	V	e	270	VI	e
171	IV	f	221	V	f	271	VI	f
172	IV	g	222	V	g	272	VI	g
173	IV	h	223	V	h	273	VI	h
174	IV	i	224	V	i	274	VI	i
175	IV	j	225	V	j	275	VI	j
176	IV	k	226	V	k	276	VI	k
177	IV	l	227	V	l	277	VI	l
178	IV	m	228	V	m	278	VI	m
179	IV	n	229	V	n	279	VI	n
180	IV	o	230	V	o	280	VI	o
181	IV	p	231	V	p	281	VI	p
182	IV	q	232	V	q	282	VI	q
183	IV	r	233	V	r	283	VI	r
184	IV	s	234	V	s	284	VI	s
185	IV	t	235	V	t	285	VI	t
186	IV	u	236	V	u	286	VI	u
187	IV	v	237	V	v	287	VI	v
188	IV	w	238	V	w	288	VI	w
189	IV	x	239	V	x	289	VI	x
190	IV	y	240	V	y	290	VI	y
191	IV	z	241	V	z	291	VI	z
192	IV	aa	242	V	aa	292	VI	aa
193	IV	ab	243	V	ab	293	VI	ab
194	IV	ac	244	V	ac	294	VI	ac
195	IV	ad	245	V	ad	295	VI	ad
196	IV	ae	246	V	ae	296	VI	ae
197	IV	af	247	V	af	297	VI	af
198	IV	ag	248	V	ag	298	VI	ag
199	IV	ah	249	V	ah	299	VI	ah
200	IV	ai	250	V	ai	300	VI	ai
201	IV	aj	251	V	aj	301	VI	aj
202	IV	ak	252	V	ak	302	VI	ak
203	IV	al	253	V	al	303	VI	al
204	IV	am	254	V	am	304	VI	am
205	IV	an	255	V	an	305	VI	an
206	IV	ao	256	V	ao	306	VI	ao
207	IV	ap	257	V	ap	307	VI	ap
208	IV	aq	258	V	aq	308	VI	aq
209	IV	ar	259	V	ar	309	VI	ar
210	IV	as	260	V	as	310	VI	as
211	IV	at	261	V	at	311	VI	at

Ex#	Core	R	Ex#	Core	R	Ex#	Core	R
212	IV	au	262	V	au	312	VI	au
213	IV	av	263	V	av	313	VI	av
214	IV	aw	264	V	aw	314	VI	aw
215	IV	ax	265	V	ax	315	VI	ax

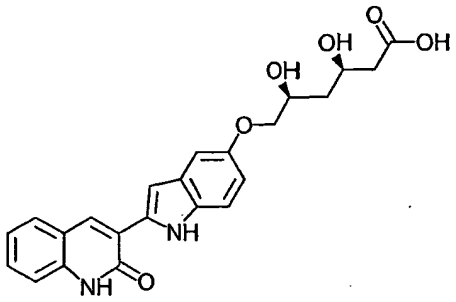
In the above table, R is selected from the following radicals:





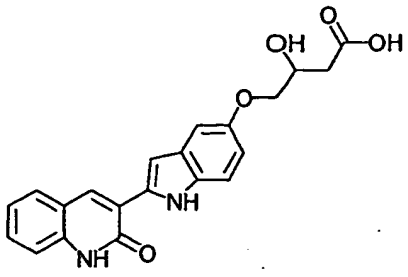
These amide examples **16 - 315** can be made by those skilled in the art following the above procedure and/or known procedures.

Example 316: (3R,5S)-3,5-Dihydroxy-6-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-yloxy]-hexanoic acid



The title compound can be made by those skilled in the art following known procedures.

Example 317: 3-Hydroxy-4-[2-(2-oxo-1,2-dihydro-quinolin-3-yl)-1H-indol-5-yloxy]-butyric acid



The title compound can be made by those skilled in the art following known procedures.

VEGFR Biochemical Assay

The compounds were assayed for biochemical activity by Upstate Ltd at Dundee, United Kingdom, according to the following procedure. In a final reaction volume of 25 µl, KDR (h) (5-10 mU) is incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.33 mg/ml myelin basic protein, 10 mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 5 µl of a 3% phosphoric acid solution. 10 µl of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

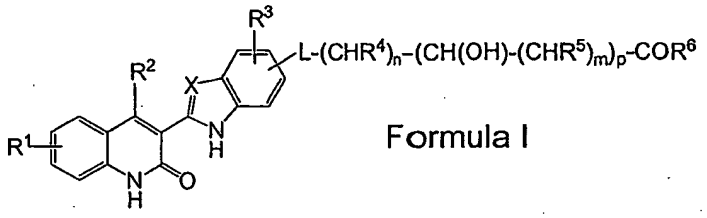
Compounds of the present invention were tested in this assay and exhibited IC_{50} between 1 – 5,000 nM.

Cellular Assay: HUVEC: VEGF induced proliferation

The compounds were assayed for cellular activity in the VEGF induced proliferation of HUVEC cells. HUVEC cells (Cambrex, CC-2517) were maintained in EGM (Cambrex, CC-3124) at 37°C and 5% CO_2. HUVEC cells were plated at a density 5000 cells/well (96 well plate) in EGM. Following cell attachment (1hour) the EGM-medium was replaced by EBM (Cambrex, CC-3129) + 0.1% FBS (ATTC , 30-2020) and the cells were incubated for 20 hours at 37°C. The medium was replaced by EBM +1% FBS, the compounds were serial diluted in DMSO and added to the cells to a final concentration of 0 – 5,000 nM and 1% DMSO. Following a 1 hour pre-incubation at 37°C cells were stimulated with 10ng/ml VEGF (Sigma, V7259) and incubated for 45 hours at 37°C. Cell proliferation was measured by BrdU DNA incorporation for 4 hours and BrdU label was quantitated by ELISA (Roche kit, 16472229) using 1M H_2SO_4 to stop the reaction. Absorbance was measured at 450nm using a reference wavelength at 690nm.

What is claimed is:

1. A compound of Formula (I):



Formula I

wherein:

R^1 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, (C1-C6) alkoxy, amino, (C1-C6) alkylamino, amide, sulfonamide, cyano, substituted or unsubstituted (C6-C10) aryl;

R^2 is selected from the group consisting of hydrogen, halo, (C1-C6) alkyl, (C3-C8) cycloalkyl, (C1-C6) haloalkyl, hydroxy, alkoxy, (C1-C6) alkoxy(C1-C6) alkyl, amino, (C1-C6) alkylamino, (C6-C10) arylamino;

R^3 is selected from the group consisting of hydrogen, (C1-C6) alkyl, halo, cyano;

R^4 is selected from the group consisting of hydrogen and (C1-C6) alkyl;

R^5 is selected from the group consisting of hydrogen, (C1-C6) alkyl and hydroxyl;

R^6 is selected from the group consisting of hydroxyl, O-(C1-C6) alkyl, O-(C3-C8) cycloalkyl, substituted or unsubstituted O-(C6-C10) aryl, and NR^7R^8; where R^7 and R^8 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C9) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or R^7 and R^8 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids; and

n and **m** are independently 0, 1, 2, or 3; **p** is 1, 2, or 3;

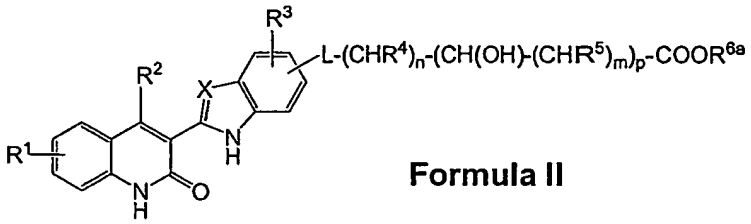
X is selected from the group consisting of CR^9 and N; where R^9 is selected from the group consisting of hydrogen, halo, and (C1-C6) alkyl;

L is a divalent linker selected from the group consisting of -O-, -NR^{10}-, -C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{11}-, -CHR^{10}-NR^{11}-, -CHR^{10}-NR^{11}-C(O)-NR^{12}-, -$S(O_2)$-NR^{10}-, -O-CHR^{10}-C(O)-NR^{11}-, and -CH_2-CH_2-NR^{10}-;

R^{10}, R^{11}, and R^{12} are independently is selected from the group consisting of hydrogen and (C1-C6) alkyl;

or, a pharmaceutically acceptable salt, its tautomer, a pharmaceutically acceptable salt of its tautomer, or a prodrug thereof.

2. The compound, salt, tautomer, or prodrug according to claim 1 represented by Formula (II):



Formula II

wherein:

R^{6a} is selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, and substituted or unsubstituted (C6-C10) aryl.

3. The compound, salt, tautomer, or prodrug according to claim 2, wherein:

X is selected from the group consisting of CH and N;

R^1 is selected from the group consisting of hydrogen, halo, and cyano;

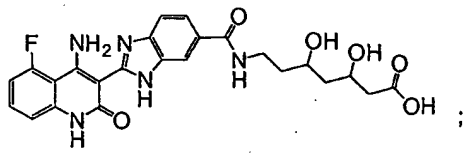
R^2 is selected from the group consisting of hydrogen, hydroxyl, (C1-C6)alkoxy, -NH_2, and -NHR^{13}, where R^{13} is (C1-C6)alkyl;

R^4, R^5 and R^{6a} are hydrogen;

n, and **p** are independently 1, or 2; **m** is 0 or 1;

L is selected from the group consisting of -C(O)-NR^{10}-, -NR^{10}-C(O)-NR^{11}-, -CHR^{10}-NR^{11}-C(O)-NR^{12}-, -O-CHR^{10}-C(O)-NR^{11}-, -$S(O_2)$-NR^{10}-; where R^{10}, R^{11} and R^{12} are independently hydrogen and (C1-C6)alkyl.

4. The compound, salt, tautomer, or prodrug according to claim 2 selected from the group represented by the following structures: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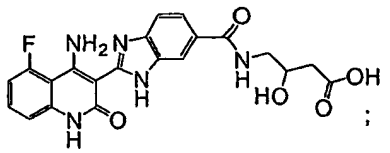
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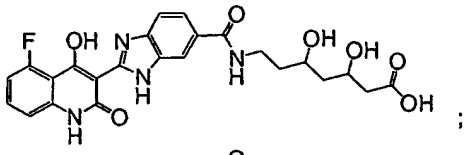
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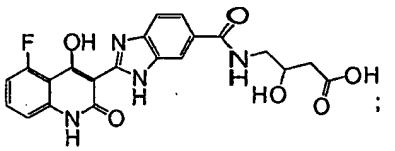
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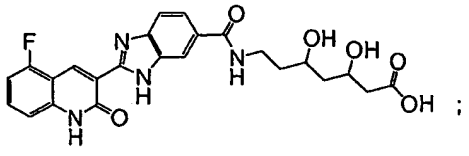
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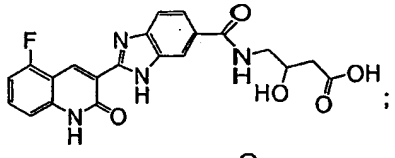
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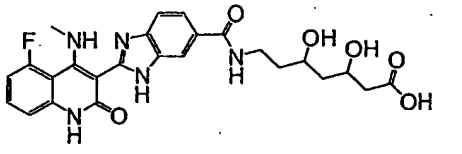
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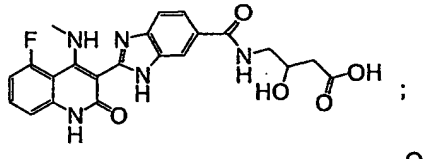
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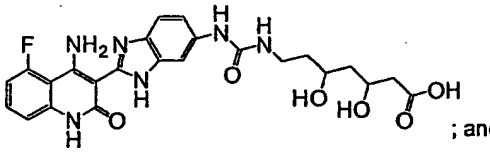
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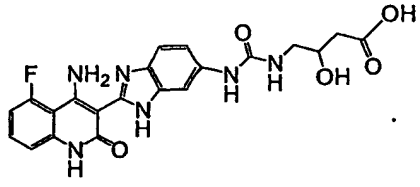
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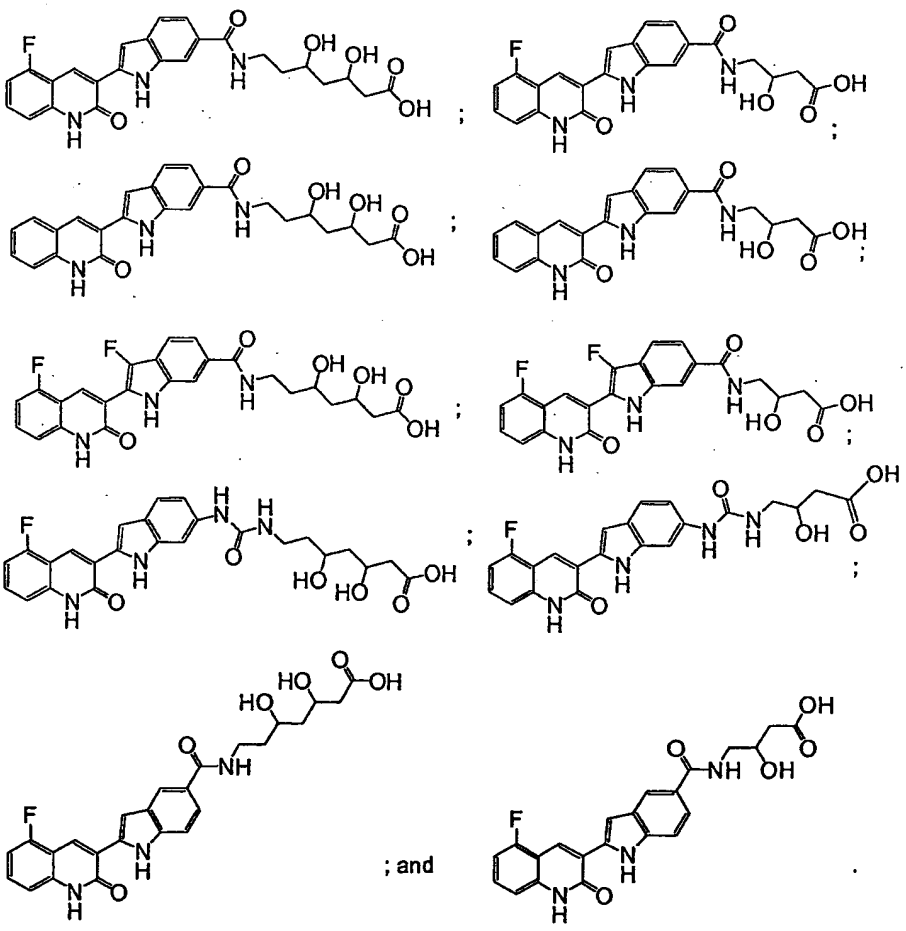
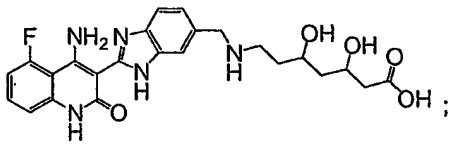
5. The compound, salt, tautomer, or prodrug according to claim 2 selected from the group represented by the following structures:



; and

6. The compound, salt, tautomer, or prodrug according to claim 2 selected from the group represented by the following structures: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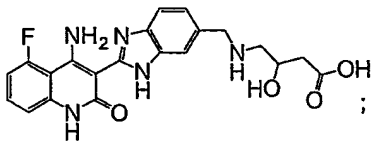
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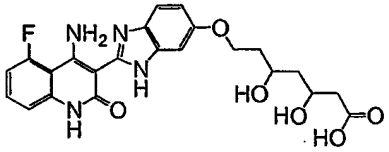
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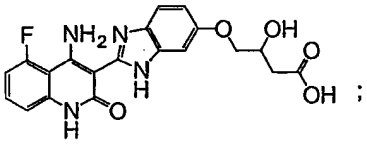
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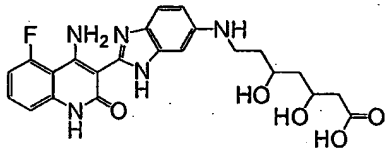
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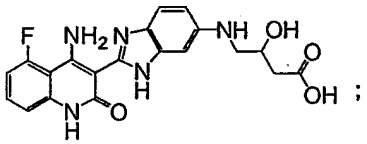
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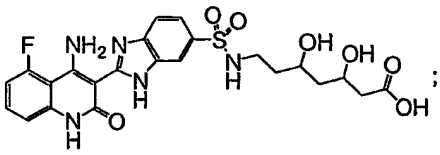
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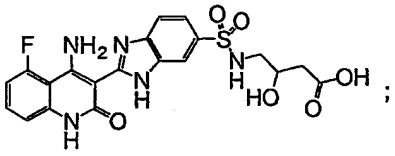
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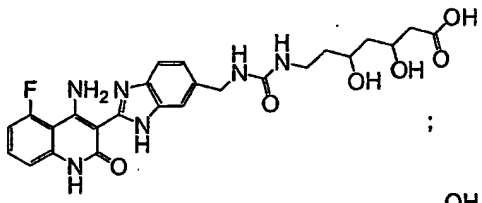
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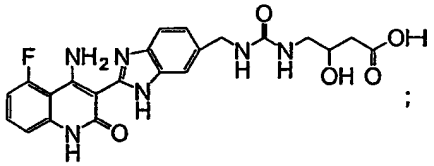
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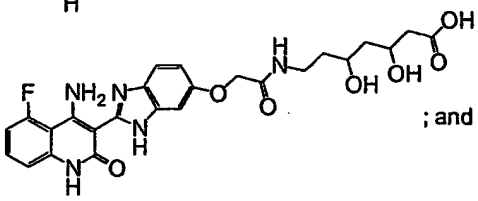
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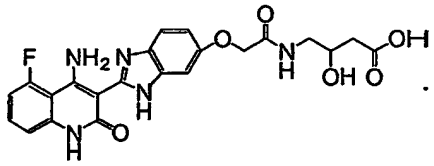
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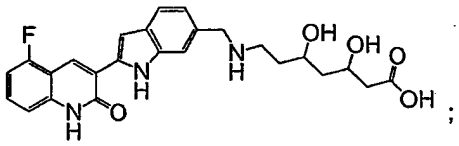
7. The compound, salt, tautomer, or prodrug according to claim 2 selected from the group represented by the following structures: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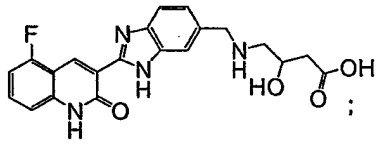
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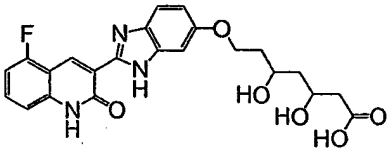
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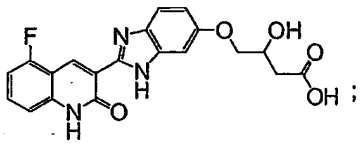
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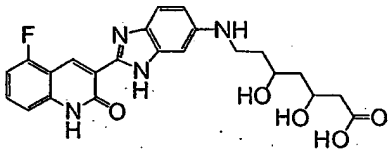
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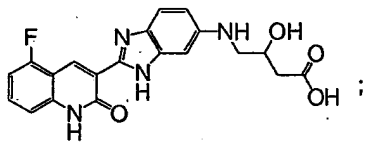
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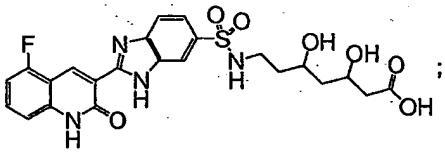
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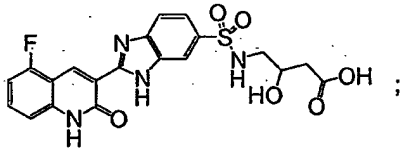
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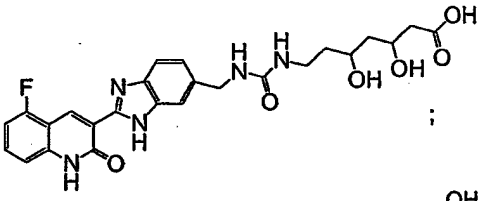
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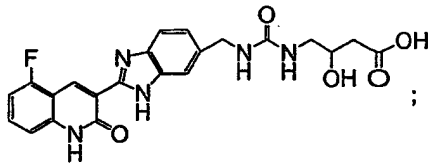
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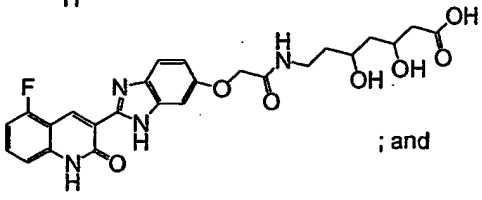
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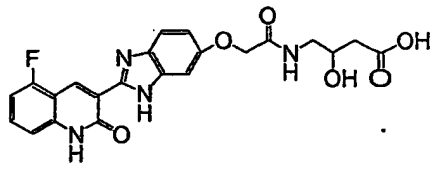
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8. The compound, salt, tautomer, or prodrug according to claim 1 wherein R^6 is NR^7R^8.

9. A compound, salt, tautomer, or prodrug according to claim 8 wherein

X is selected from the group consisting of CH and N;

R^1 is selected from the group consisting of hydrogen, halo, and cyano;

R^2 is selected from the group consisting of hydrogen, hydroxyl, (C1-C6)alkoxy, $-NH_2$, and $-NHR^{13}$, where R^{13} is (C1-C6)alkyl;

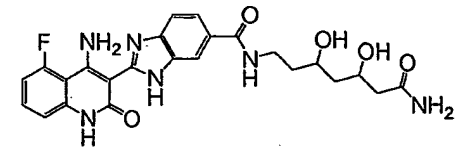
R^4, R^5 and R^6 are hydrogen;

n, and **p** are independently 1, or 2; **m** is 0 or 1;

L is selected from the group consisting of $-C(O)-NR^{10}-$, $-NR^{10}-C(O)-NR^{11}-$, $-CHR^{10}-NR^{11}-C(O)-NR^{12}-$, $-O-CHR^{10}-C(O)-NR^{11}-$,,$-S(O_2)-NR^{10}-$; where R^{10}, R^{11} and R^{12} are independently hydrogen and (C1-C6)alkyl; and

R^7 and $R^8$are selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) hydroxyalkyl, (C1-C6) dihydroxyalkyl, (C1-C6) alkoxy , (C1-C6) alkyl carboxylic acid, (C1-C6) alkyl phosphoric acid, (C1-C6) alkyl sulfuric acid, (C1-C6) hydroxyalkyl carboxylic acid, (C1-C6) alkyl amide, (C3-C8) cycloalkyl, (C5-C8) heterocycloalkyl, (C6-C10) aryl, (C5-C9) heteroaryl, (C3-C8) cycloalkyl carboxylic acid, or $R^7$and R^8 together with N forms a (C5-C8) heterocyclic ring either unsubstituted or substituted with one or more hydroxyls, ketones, ethers, and carboxylic acids.

10. The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures: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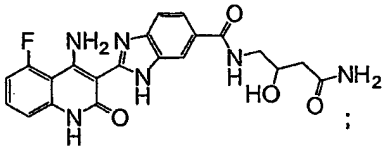
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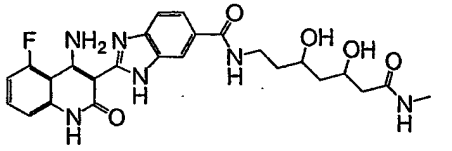
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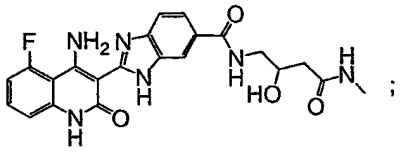
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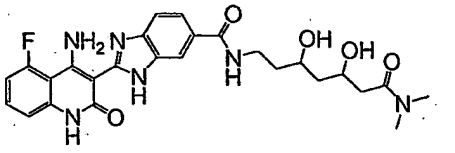
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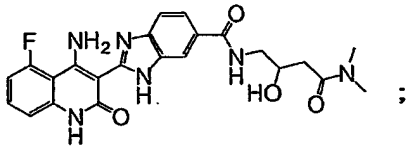
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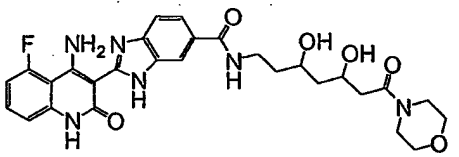
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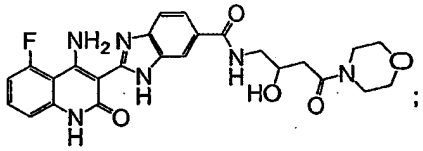
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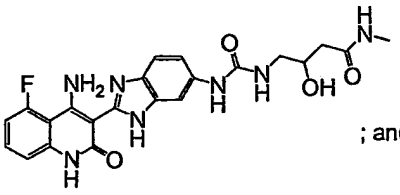
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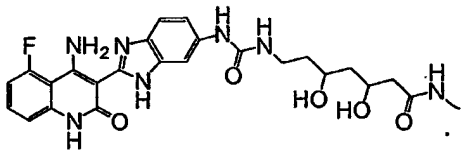
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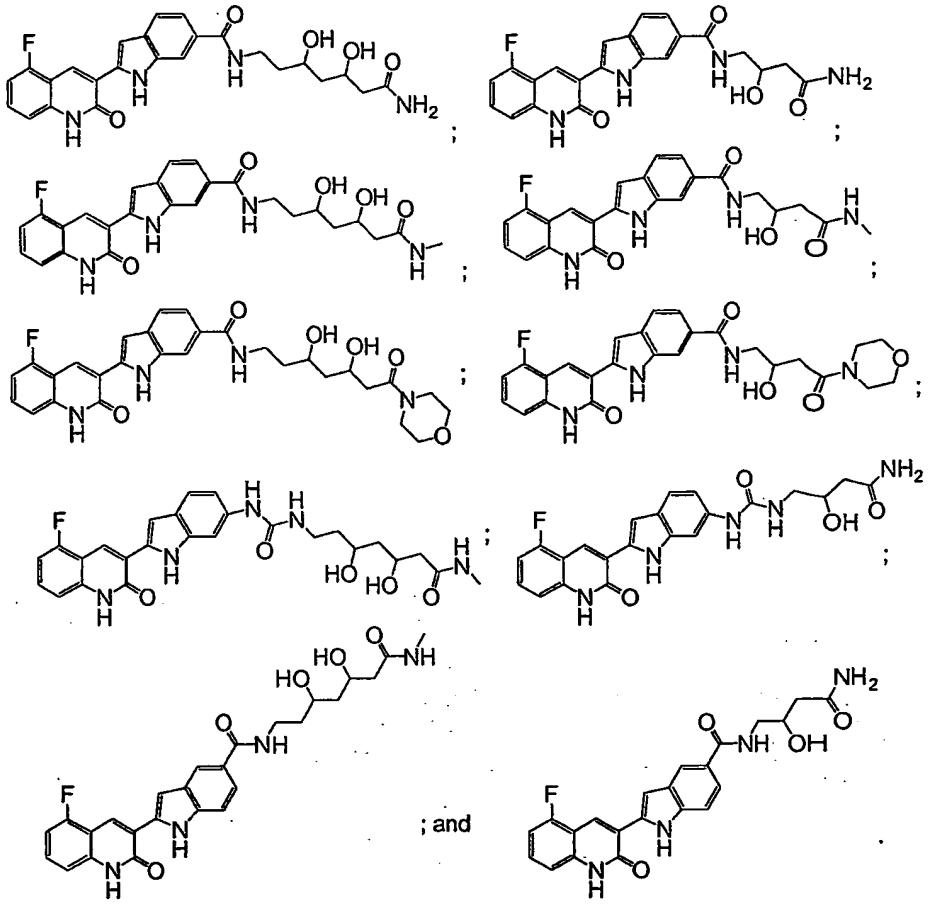
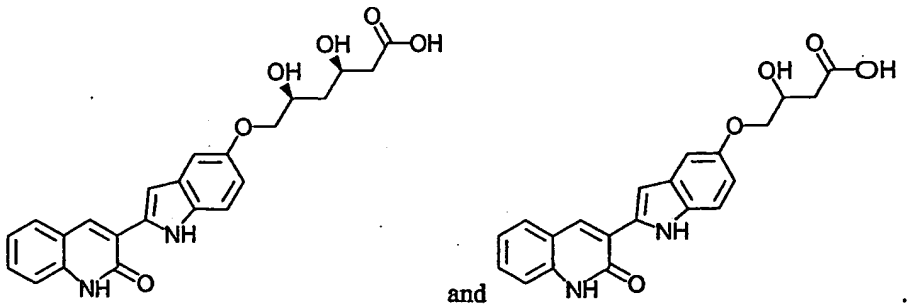
11. The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:



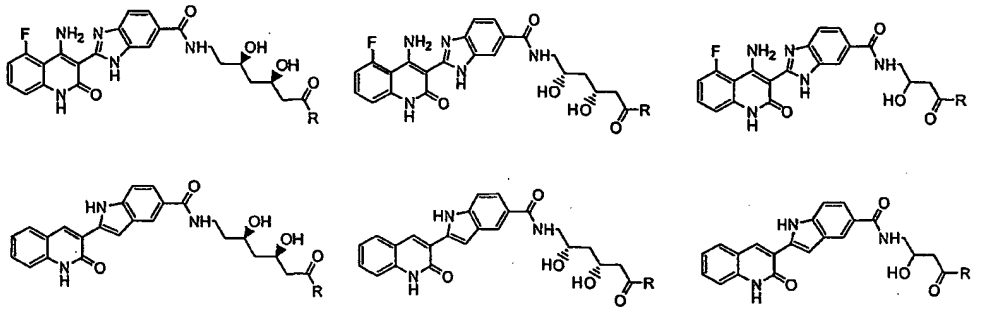
; and

12. The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:



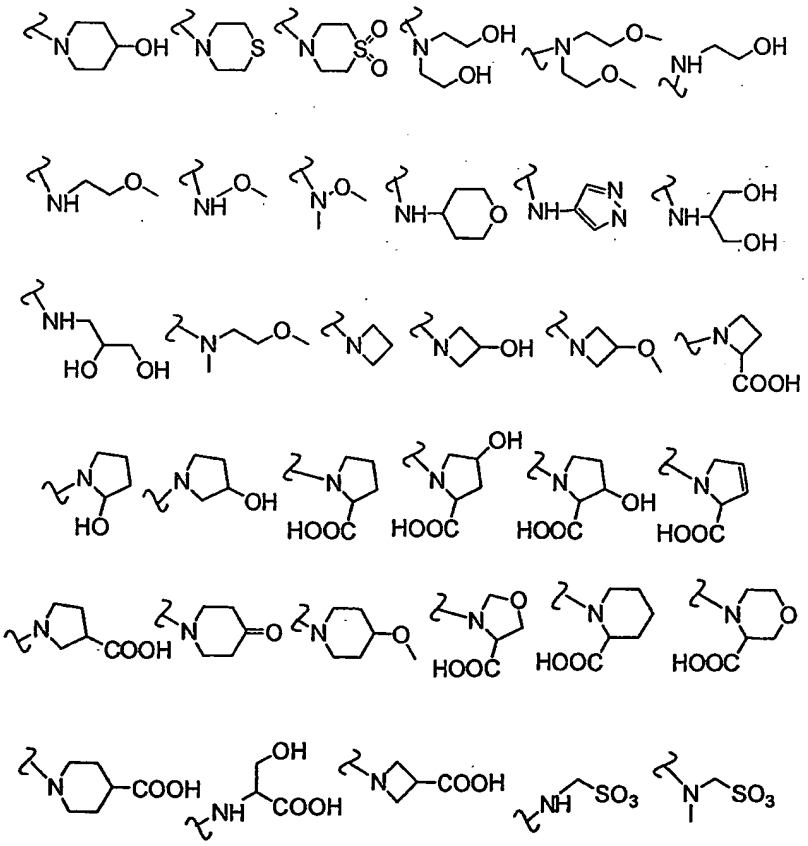
and

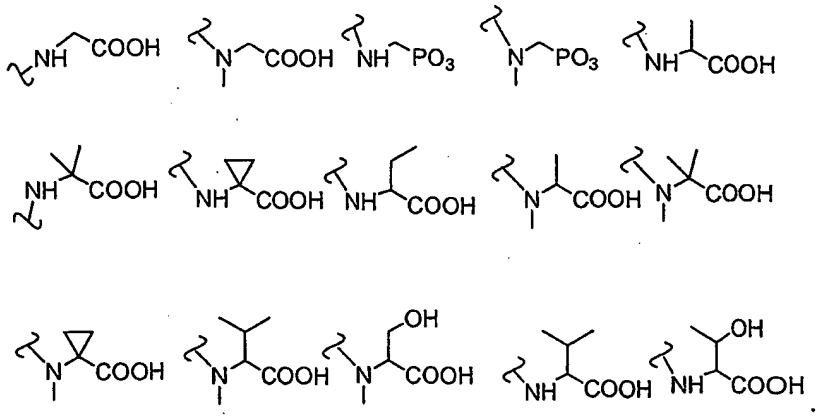
13. The compound, salt, tautomer, or prodrug according to claim 8 selected from the group represented by the following structures:



wherein:

R is selected from the group consisting of radicals represented by the following structures:





14. The compound, salt, tautomer, or prodrug according to any of claims 1-13 with the following provisios:

the compound, salt, tautomer, or prodrug of claim 2 is excluded or
the compound, salt, tautomer, or prodrug of claim 3 is excluded or
the compound, salt, tautomer, or prodrug of claim 4 is excluded or
the compound, salt, tautomer, or prodrug of claim 5 is excluded or
the compound, salt, tautomer, or prodrug of claim 6 is excluded or
the compound, salt, tautomer, or prodrug of claim 7 is excluded or
the compound, salt, tautomer, or prodrug of claim 8 is excluded or
the compound, salt, tautomer, or prodrug of claim 9 is excluded or
the compound, salt, tautomer, or prodrug of claim 10 is excluded or
the compound, salt, tautomer, or prodrug of claim 11 is excluded or
the compound, salt, tautomer, or prodrug of claim 12 is excluded or
the compound, salt, tautomer, or prodrug of claim 13 is excluded.

15. A method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of claims 1-14.

16. The method of claim 15, wherein said protein kinase is selected from the group consisting of VEGF receptors, PDGF receptors.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/40346

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/47, 31/44; C07D 215/16, 215/20, 491/02, 471/02
US CL : 514/312, 313, 314; 546/153, 157, 135, 116
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/312, 313, 314; 546/153, 157, 135, 116

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, WEST, STN: Registry, Chemical Abstracts

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,774,237 A (RENHOWE et al) 10 August 2004 (10.08.2004), claims.	1-16
A	US 6,479,512 A (FRALEY et al) 12 November 2002 (12.11.2002), claims.	1-16
A	US 6,306,874 A (FRALEY et al) 23 October 2001 (23.10.2001), claims.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
31 March 2005 (31.03.2005)

Date of mailing of the international search report
13 APR 2005

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Form PCT/ISA/210 (second sheet) (January 2004)